Peer-Review comments and authors responses

"Open-Label Placebo effects in reducing depression severity among adults with major depressive disorder: A Systematic Review"

Dear editor and Reviewer,

Thank you for the opportunity to review our manuscript for consideration in Principles and Practice of Clinical Research. We considered all the suggested points to improve the quality of the manuscript. Please find below point-by-point answers to the recommendations.

Reviewer 1

Abstract

1. **Comment:** The abstract is well-written and structured. However, since the sample size is small and the majority of the participants are women, the conclusions here might overestimate the findings. Consider acknowledging the generalizability limitations and highlighting OLP may present a promising approach instead of a 'feasible treatment option' for MDD. This was well-explained in the manuscript, but the same idea should be included in the abstract.

Response: *We revised the abstract to acknowledge the small sample size and predominance of female participants and tempered the conclusion to state that open-label placebo (OLP) may represent a promising approach rather than a feasible treatment option for major depressive disorder, thereby addressing limitations in generalizability.*

Introduction

2. **Comment:** Consider splitting the ideas here into two or three sentences for better readability

Response: *We split the original sentence into multiple shorter sentences to improve readability and clarity.*

3. **Comment:** This sentence feels abrupt. I suggest changing it to something like: -Beyond its impact on quality of life and productivity, it is also associated with an elevated risk of premature death, largely due to suicide and comorbid medical conditions. This allows a smoother transition to the new concept -mortality- presented.

Response: *We rephrased the sentence to provide a smoother transition to the concept of mortality, explicitly linking depression to premature death due to suicide and comorbid medical conditions.*

4. **Comment:** This sentence is too long and tries to cover frequency, examples of mild effects, examples of severe effects, and impact on adherence all at once. Consider breaking it in two shorter sentences to improve readability.

Response: *We divided the sentence into two shorter sentences to separately address adverse effect frequency and severity, and their impact on treatment adherence.*

5. **Comment:** The use of "However" as a connector does not flow with the idea presented in the paragraph. Consider replacing it with a smoother connector, such as "In this context" or "Given these limitations," to maintain coherence.

Response: *We replaced "However" with a smoother contextual connector to improve coherence within the paragraph.*

6. **Comment:** Consider replacing the phrase 'it has been reported' for more clarity on the subject 'it'. It can sound like secondhand information rather than direct evidence. In addition, replace 'control trials' with 'controlled trials'

Response: *We revised the phrasing to clearly identify the subject instead of using "it has been reported" and corrected "control trials" to "controlled trials."*

7. **Comment:** Missing space before parentheses.

Response: *We corrected the missing space before the parentheses.*

8. **Comment:** I suggest rephrasing the paragraph for better readability "Systematic reviews have reported positive effects of OLP in conditions including irritable bowel syndrome, depression, allergic rhinitis, back pain, ADHD, induced pruritus, cancer-related fatigue, and menopausal hot flashes."

Response: *We rephrased the paragraph to improve readability and concisely list conditions in which OLP has shown positive effects.*

9. **Comment:** Missing space before parentheses.

Response: *We corrected the missing space before the parentheses.*

10. **Comment:** Needs rephrasing. The phrase seems incomplete and does not connect with the following sentence.

Response: *We rephrased the sentence to ensure completeness and improve its logical connection with the subsequent sentence.*

<u>Methods</u>

11. **Comment:** The repetition of TAU sounds confusing. Consider replacing it with "OLP or OLP+TAU versus TAU alone."

Response: *We revised the wording to clearly distinguish comparator groups by replacing repeated references to TAU with "OLP or OLP + TAU versus TAU alone."*

12. **Comment:** "Clinical Trials" → specify "ClinicalTrials.gov" for accuracy).

Response: *We specified "ClinicalTrials.gov" instead of "Clinical Trials" for accuracy.*

13. **Comment:** Here, it was noted that disagreements were resolved by consensus during data extraction, but the previous sentence 'team meetings were held to resolve disagreements,' is vague. I suggest specifying 'by consensus' in that first instance as well, to keep the description consistent across screening and extraction.

Response: *We revised the text to consistently state that disagreements were resolved by consensus during both screening and data extraction.*

14. **Comment:** The Selection and Data Extraction section is generally clear and appropriate. However, I suggest reevaluating the phrasing around time. It does not seem relevant to include the timing between searching and saving the articles — please check. It would also strengthen transparency to specify the exact number of reviewers per screening stage, and whether screening was performed in duplicate.

Response: *We removed unnecessary references to timing between searching and saving articles, clarified the number of reviewers involved at each screening stage, and specified that screening was performed in duplicate.*

15. **Comment:** Consider rephrasing: Selected clinical trials were summarized in Microsoft Excel tables… for a smoother beginning.

Response: *We rephrased the sentence to improve flow and clarity at the beginning of the data synthesis paragraph.*

16. **Comment:** Replace 'Team meetings' with the actual process taken; consensus? Fourth reviewer involved if no consensus?

Response: *We replaced the vague reference to "team meetings" with a clear description of the consensus-based resolution process.*

Results

17. **Comment:** Redundant.

Response: *We removed the redundant text to improve clarity and conciseness.*

18. **Comment:** "Schienele et. al" → should be "Schienle et al." Extra e and extra period.

Response: *We corrected the author name to "Schienle et al." by removing the extra letter and punctuation.*

19. **Comment:** "Schienle et. al" → should be "Schienle et al." same correction as before.

Response: *We corrected the author name consistently throughout the Results section.*

20. **Comment:** Missing an 'a' before statistically.

Response: *We added the missing article before "statistically."*

21. **Comment:** The highlight sounds confusing, and the last sentence is redundant. Needs rephrasing to improve readability.

Response: *We rephrased the highlighted text to improve readability and removed the redundant sentence.*

22. **Comment:** Missing 'the' before main.

Response: *We added the missing article before "main."*

23. **Comment:** The point here, splitting the idea in two sentences does not seem appropriate since they are strongly related. Consider rephrasing for better cohesiveness.

Response: *We rephrased the sentence to improve cohesiveness while preserving the close relationship between the ideas.*

24. **Comment:** Should be "Schienle et al." Extra e.

Response: *We corrected the author name to "Schienle et al."*

25. **Comment:** I suggest using the same formatting throughout the manuscript, E.g, 'Schienle et al.,'

Response: *We standardized citation formatting throughout the manuscript for consistency.*

26. **Comment:** Consider replacing 'the intervention' for 'OLP'.

Response: *We replaced "the intervention" with "OLP" to improve clarity and precision.*

Discussion

27. Comment: Missing article "…this is the first systematic review…"
Response: *We added the missing article to correct the sentence ("this is the first systematic review").*

28. Comment: Consider rephrasing.
Response: *We rephrased the sentence to improve clarity and readability.*

29. Comment: Inconsistent reference formatting "Kelley et. al" → should be "Kelley et al."
Response: *We corrected the reference formatting to "Kelley et al." consistently.*

30. Comment: Potential dilution" sounds speculative, consider rephrasing.
Response: *We rephrased the statement to avoid speculative language while preserving the intended meaning.*

31. Comment: Redundant. I suggest choosing one of them, 'practical value' or 'clinical significance'.
Response: *We removed redundancy by retaining a single term and clarifying its meaning.*

32. Comment: Depression symptoms.
Response: *We revised the wording to explicitly refer to depression symptoms.*

33. Comment: "Nitzan et. al" → should be "Nitzan et al."
Response: *We corrected the reference formatting to "Nitzan et al."*

34. Comment: Enhances.
Response: *This sentences was rephrased.*

35. Comment: Consider rephrasing for simplicity and to avoid wordiness "Risk of bias was also a concern…
Response: *We rephrased the sentence to reduce wordiness and improve clarity.*

36. Comment: "Schienle et. al" → should be "Schienle et al."
Response: *We corrected the reference formatting to "Schienle et al."*

37. **Comment:** The statement 'may also enhance' sounds too strong for results seen only in one study. I suggest considering another phrase, such as 'preliminary evidence suggests.

Response: *We tempered the language to reflect that findings were based on a single study and now describe them as preliminary evidence.*

Reviewer 2

Title

1. **Comment:** Is it just systematic review, or meta-analysis too?

Response: *We clarified the title to accurately reflect the scope of the study, specifying that this work is a systematic review with meta-analysis.*

Abstract

2. **Comment:** Which databases?

Response: *We specified the databases searched in the abstract to improve transparency (Cochrane, PsycNet, PMC, ClinicalTrials.gov, Scopus, PubMed).*

3. **Comment:** ...including studies from X to May Y, 2025

Response: *We added the date of the literature search, specifying that studies published up to May 5, 2025, were included.*

Methods

4. **Comment:** Did you include more filters other than english language, like year of publication?

Response: *We clarified that no additional filters beyond English language were applied, and that studies were not restricted by year of publication.*

5. **Comment:** Can you describe more in depth how was managed the divergences?

Response: *We expanded the Methods section to describe in greater detail how disagreements were managed, specifying independent screening, resolution by consensus, and involvement of a third reviewer when necessary.*

Conclusion

6. **Comment:** In general, the reader understands in Results and Discussion that this is a promising field for future studies and in-depth research. But you won't want to take a position. So the unbiased conclusion is what actually you can clearly state with the current evidence available. For example: there are few studies; heterogeneous; not generalizable; and at this moment there is no evidence that OLP can reduce depression scores in adults with MDD.

Response: *We revised the Conclusion to adopt a more cautious and unbiased tone, explicitly emphasizing the limited number of studies, heterogeneity across trials, and lack of generalizability. We clarified that, based on the current evidence, there is insufficient evidence to conclude that open-label placebo reduces depressive symptoms in adults with major depressive disorder.*

Reviewer 3

Introduction

1. **Comment:** Line 71-74: Sentence structure is too long. Also, please ensure that all references are accurate and verifiable, as errors may arise from reliance on automated tools. Here I was unable to access the cited website to verify. "Major depressive disorder (MDD), also referred to as major depression or clinical depression, is a common and disabling mental illness characterized by persistent sadness and a loss of interest or pleasure in previously enjoyable activities. It affects 5% of adults worldwide, approximately 280 million people, and more than 75% of people in low- and middle-income countries do not receive treatment (WHO, 2023)."

Response: *We revised the sentence by splitting it into shorter statements to improve readability and verified that all references were accurate, accessible, and correctly cited.*

2. **Comment:** Line 75-77: This sentence could be rephrased to improve continuity, and the dashes (—) should be removed (throughout the manuscript). "During the COVID-19 pandemic in 2020, the global burden of depression increased sharply, with an estimated 27.6% rise in cases, equivalent to 53.2 million additional cases, resulting in a prevalence of about 3.2% (Collaborators, 2021)"

Response: *We rephrased the sentence to improve continuity and removed dashes throughout the manuscript for consistency.*

3. **Comment:** Line 78-71: In this section, the level of burden is addressed through three main points; however, it is currently conveyed across five short sentences. It may be better to restructure this portion into a more concise and cohesive format.

Response: *We restructured this section into a more concise and cohesive format by consolidating related ideas while preserving the key points regarding disease burden.*

4. **Comment:** Transitions between ideas (e.g., from antidepressant limitations to the promise of OLP) could be smoothed to ensure a more natural progression.

Response: *We revised transitional language to ensure a smoother progression from the limitations of antidepressant treatments to the rationale for exploring open-label placebo.*

5. **Comment:** The literature background on OLP is comprehensive, citing prior systematic reviews and meta-analyses across a range of conditions. Still, it may be useful to highlight more explicitly why depression represents a particularly important and unique context for evaluating OLP, given the chronicity, treatment resistance, and stigma associated with pharmacological options (maybe even psychological aspect of it).

Response: *We expanded the rationale to explicitly explain why depression represents a particularly important context for evaluating open-label placebo, emphasizing chronicity, treatment resistance, and psychosocial considerations.*

6. **Comment:** Improve smooth transition between essential points eg: "Given these limitations of standard care, non-pharmacological interventions such as OLP may offer a low-risk alternative."

Response: *We revised the transition sentence to improve clarity and ensure a smoother connection between* the limitations of standard care and the introduction of OLP.

Methods

1. **Comment:** Line 110: Reference is incomplete ("Higgins" only) — should be cited properly (Higgins et al., 2024) in APA 7th ed.

Response: *We corrected the reference to properly cite properly (Higgins et al., 2024) in accordance with APA 7th edition guidelines.*

2. **Comment:** Line 113: "Conducted between April and June 2025" could be clearer; does this refer to literature searches only, or the entire systematic review process? For systematic reviews, it is generally recommended to report the date when the systematic literature search commenced. Including this information would enhance transparency and reproducibility.

Response: *We clarified that the reported dates refer to the systematic literature search period and specified the date on which the search commenced.*

3. **Comment:** As you mention that a protocol was maintained, it may strengthen the manuscript to indicate whether it was registered in PROSPERO, and if so, to provide the registration details.

Response: *We clarified that the review protocol was developed a priori but was not registered in PROSPERO, and explicitly stated this in the Methods section.*

4. **Comment:** Line 118: It is not strictly necessary to restate the research question under the Search Strategy section, as this may be repetitive. You may consider directly describing the search terms, databases, and methods to streamline the section.

Response: *We streamlined the Search Strategy section by removing repetition of the research question and focusing directly on databases searched, search terms, and methods.*

5. **Comment:** Line 122: PsyNet' appears to be a typographical error; the correct database is PsycINFO. Additionally, PubMed and PubMed Central (PMC) are distinct resources (PubMed provides citations and abstracts, whereas PMC is a full-text repository). I note that in the Supplementary Table, only PubMed searches are listed. Please clarify whether PMC or other databases were actually searched.

Response: *We corrected "PsyNet" to "PsycINFO" and clarified that PubMed was searched, while PubMed Central was not used as a separate database.*

6. **Comment:** Line 122: Clinical Trials ◊ Clinicaltrials.gov

Response: *We corrected "Clinical Trials" to "ClinicalTrials.gov" for accuracy.*

7. **Comment:** Line 131: The citation for Covidence appears incomplete/incorrect ((n.d.), May 18, 2025). Consider providing a proper reference or removing unnecessary date parentheses. Kellermeyer, L., Harnke, B., & Knight, S. (2018). Covidence and Rayyan. Journal of the Medical Library Association, 106(4). https://doi.org/10.5195/jmla.2018.513

Response: *We corrected and completed the citation for Covidence and removed unnecessary date formatting.*

8. **Comment:** Some sentences are long and could be broken into shorter sentences to improve clarity (e.g., the first paragraph describing the review process).

Response: *We revised long sentences in the Methods section, particularly those describing the review process, to improve clarity and readability.*

9. **Comment:** "Six reviewers, working in pairs (two per study)" could benefit from clarification: does this mean each study was independently extracted by two reviewers, or each reviewer handled multiple studies? PRISMA guideline and Cochrane Handbook suggests two independent reviewers for a single study. Keep the data selection process straight forward and simple:

"All authors were involved in the review process. Two reviewers conducted the initial search for articles. A third reviewer intervened if there was a disagreement regarding eligibility, and a consensus was reached. The reviewers independently screened the titles and abstracts after removing duplicates in the Covidence web-based platform (Kellermeyer et al., 2018). Subsequently, full texts were reviewed if a paper was considered relevant based on the inclusion and exclusion criteria."

Response: *We clarified the reviewer workflow to align with PRISMA and Cochrane recommendations, specifying that studies were independently screened and extracted by two reviewers, with disagreements resolved by consensus involving a third reviewer.*

10. **Comment:** The exclusion of Kelley's pilot study is mentioned abruptly without explanation. Clarifying why it was excluded (e.g., insufficient data, methodological differences) would improve transparency.

Response: *We added a brief explanation clarifying the exclusion of Kelley's pilot study to improve transparency.*

11. **Comment:** It is not specified whether a fixed-effects or random-effects model was used; this is important for interpretation.

Response: *We explicitly stated that a random-effects model was used for the meta-analysis.*

12. **Comment:** Line 161-163: Providing detailed explanations of the domains of the Risk of Bias tool is not necessary. Instead, you could mention that, following Cochrane's recommendations, a traffic light plot was created manually using Excel to visually summarize the risk-of-bias assessments.

Response: *We simplified the Risk of Bias section by removing detailed domain explanations and stating that a traffic-light plot was created manually using Excel following Cochrane recommendations.*

13. **Comment:** Line 177: The current figure label 'PRISMA Flow diagram for the new systematic review' could be revised to be more descriptive "Figure 1. PRISMA flowchart illustrating the identification, screening, and inclusion of studies in the systematic review."

Response: *We revised the figure caption to a more descriptive title that clearly reflects the identification, screening, and inclusion process.*

Results

14. **Comment:** Throughout this section in text citation and narrative citation should be revised according to APA 7th ed format.

Response: *We revised all narrative and in-text citations in the Results section to ensure consistency with APA 7th edition formatting.*

15. **Comment:** In Table 1, under the 'Study Design' column, it is not necessary to label the studies as 'RCT.' Instead, specifying the design type as 'Parallel' or 'Parallel: Crossover' would more accurately describe the study structure and improve clarity for readers.

Response: *We revised Table 1 by replacing "RCT" with more precise descriptors of study structure (e.g., "Parallel" or "Parallel: Crossover").*

16. **Comment:** Line 207: To avoid ambiguity, it would be clearer to replace 'the first two studies' with proper narrative citations. This ensures readers can easily identify which studies are being referred to and improves precision in reporting intervention details.

Response: *We replaced the phrase "the first two studies" with explicit narrative citations to avoid ambiguity.*

17. **Comment:** Line 220: Grammatical error: "and dropout rates, and other correlative relationships."

Response: *We corrected the grammatical error for clarity.*

18. **Comment:** Typically, in reporting results, the main body of evidence is presented first, followed by an assessment of study quality. In this case, with only three studies included, presenting the quality assessment first is acceptable; however, including a brief line summarizing the main findings before the quality assessment could improve readability and context for the reader.

Response: *We added a brief summary of the main findings before the risk-of-bias assessment to improve readability and context.*

19. **Comment:** Line 227-231: Currently, the section largely iterates or explains the traffic light plot. It would be more informative to provide study-specific details that contributed to each quality rating. For example, you could describe how particular methodological aspects reduced study quality: Studies with some concerns were randomized without clear information on allocation sequence or its concealment, raising concerns about the randomization process. However, Beanato et al. (2024) used pseudo-randomization, while Violante et al. (2023) and Zhang et al. (2022) used Latin square designs-despite being relatively predictable, showed no overt flaws in the randomization process, and also efforts were made to balance participants across conditions. Similarly, Piao et al. (2022) and Wang et al. (2024, 2025) provided information on baseline differences between intervention groups; no imbalances were apparent and any observed imbalances were compatible with chance. Vassiliadis et al. (2024a) provided no information regarding baseline differences between intervention groups. In addition, three studies (Thiele et al., 2024; Von Conta et al., 2022; Z. Zhu et al., 2022) reported randomization without providing any details on the allocation sequence or its concealment, introducing a high risk of bias in the randomization process. Specifically, Von Conta et al. (2022) and Zhu et al. (2022) measured baseline outcomes (IAF at resting state and baseline fMRI, respectively) before allocation, while Thiele et al. (2024) excluded over 20% of participants post-randomization (9 due to coding errors and 10 because of the absence of a discernible alpha peak during the first resting block used to determine IAF) without accounting for these exclusions in the data analysis, potentially distorting the randomization sequence.

Response: *We revised this section to include study-specific methodological details contributing to each risk-of-bias rating rather than reiterating the traffic-light plot.*

20. **Comment:** It is important to note that while the Cochrane Risk of Bias 2 (RoB2) tool was used to assess study quality, certain domains must be interpreted in the context of open-label placebo (OLP) trials. Specifically, blinding and deviations from intended interventions (D2) are inherently limited because OLP interventions are, by design, unblinded; as a result, RoB2 may flag a high risk of bias even though this is an intentional feature rather than a methodological flaw. Similarly, measurement of the outcome (D4) is often based on self-reported scales, which RoB2 may rate as high risk, but this aligns with the hypothesized psychological mechanisms of OLP and does not necessarily indicate poor study quality. Please elaborate on how this was handled.

Response: *We explicitly addressed the interpretation of RoB2 domains in the context of open-label placebo trials, clarifying that lack of blinding and self-reported outcomes reflect intentional design features rather than methodological flaws.*

21. **Comment:** Line 257: "The two other RCTs, Kelley et al. and Nitzan et al.,"◊ In Kelley et al. and Nitzan et al.

Response: *We revised the sentence to correctly use narrative citations for Kelley et al. and Nitzan et al.*

22. **Comment:** It's acceptable to conduct a meta-analysis, but the manuscript should explicitly note the limited body of evidence and interpret results cautiously.

Response: *We explicitly emphasized cautious interpretation of the meta-analysis given the limited number of included studies.*

Discussion

23. **Comment:** In academic writing, it's often recommended to start the Discussion with a clear, concise statement of your main finding. "Across the three included RCTs, open-label placebo (OLP) interventions showed a trend toward modest reductions in depressive symptoms compared with treatment-as-usual or control conditions, although not all studies reached statistical significance"

Response: *We revised the opening of the Discussion to begin with a clear and concise summary of the main findings.*

24. **Comment:** The Discussion section is exceptionally well-crafted and comprehensive. It demonstrates a strong command of the research methodology and effectively contextualizes the findings within both prior research and the broader clinical and methodological landscape.

Response: *We thank the reviewer for the positive and constructive feedback.*

Reviewer 4

Introduction

1. **Comment:** I suggest changing this phrase, or link it with the next to make it more comprehensive.

Response: *We revised the phrasing and explicitly linked it to the subsequent sentence to improve coherence and make the rationale more comprehensive.*

Methods

2. **Comment:** Year is missing in reference.

Response: *We added the missing publication year to the reference to ensure completeness and accuracy.*

3. **Comment:** Please you should specify which fatcors were considereed for the diagnosis of MDD.

Response: *We specified the diagnostic criteria used for major depressive disorder (MDD), clarifying that diagnoses were based on standardized criteria (DSM-IV, DSM-V, or ICD-10), depending on the included study. This is found in results.*

4. **Comment:** Please you should specify which fatcors were considereed for the diagnosis of MDDthe scales used to evaluate the outcome.

Response: *We clarified the outcome measurement scales used to assess depression severity, specifying*

validated instruments employed across studies (e.g., HAM-D-17, QIDS-SR16, BDI-II). This is found in results.

5. **Comment:** You should move this to the result section.

Response: *We moved the indicated content to the Results section to ensure appropriate separation between methodological description and study findings.*

Results

6. **Comment:** I suggest to only refer to results in this part. There is some interpretation, and conclusion stated, that fit more in the discussion tahn in the result section.

Response: *We revised this section to restrict content to factual reporting of results and relocated interpretative statements and conclusions to the Discussion section.*

7. **Comment:** Delete.

Response: *Sentence rephrased accordingly.*

Discussion

8. **Comment:** I suggest delete this sub-headline.

Response: *We deleted the suggested subheading to improve flow and avoid unnecessary sectioning.*

9. **Comment:** Repeated in the limitations. I would talk about the scare number of studies and small sample sizes together in only one part of the discussion.

Response: *We consolidated discussion of the limited number of studies and small sample sizes into a single section to reduce redundancy.*

10. **Comment:** I suggest delete this sub-headline.

Response: *We deleted the suggested subheading as recommended.*

11. **Comment:** I would merge all of these paraghraphs in only ione section.

Response: *We merged the indicated paragraphs into a single cohesive section to improve clarity and organization.*